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GENERAL REVIEW OF OUR PRESENT KNOWLEDGE OF THE VITAMINS*

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I.

SOME GENERAL PRINCIPLES

Knowledge of the vitamins has now become so extensive, and particularly its different branches have in recent years diverged so widely from each other, that it seems no longer possible to summarize the whole subject in a single lecture in a symmetrical or balanced fashion and at the same time explicitly enough to be of service to those who would put this knowledge to practical use.

For the purpose of the present symposium, therefore, it seems best for me to leave many important matters entirely to the other speakers, and to attempt in this talk merely (1) to emphasize those aspects of the basic science of the subject which now seem sufficiently established to be used confidently in practice, and (2) to speak very briefly on a few selected topics regarding individual vitamins whose

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significance may be of special interest to the physician—for while I am not trained in medicine, I have been especially requested to address myself this evening, in-so-far as I can, to the point of view of the practitioner. At least we can meet on the ground of a common interest in the enhancement of health.

I shall not begin by defining the vitamins. I do not know any good definition for vitamins as a group; and I think I do know some good reasons for not attempting any.

Firstly, and most fundamentally, the fact should be fully realized and constantly kept in mind, that it is only as an accidental result of their having been discovered in a more rapid succession than they could be physically isolated and chemically identified that the vitamins ever came to be grouped together and called by a group name. *They are not a natural group.* The more we learn about them the less alike do they appear, whether in chemical nature or in nutritional function.

Each vitamin is entirely specific in the sense that no one or combination of them can take the place of any other one.

While details of molecular constitution are still being worked out, enough is known of at least vitamins A, B, C, and D to show that these four substances belong to four radically different types of organic compounds.

Correspondingly, their functions in the body are radically unlike.

Whenever, then, the physician has reason to think that he may be dealing with a vitamin deficiency—or, if not with a manifest deficiency, then with a condition in which a more liberal vitamin intake would be beneficial—the question *which* vitamin becomes increasingly insistent as the unlikeness of the individual vitamins is rendered constantly clearer by current research.

And the practitioner's utilization of present scientific knowledge of the vitamins can proceed with the greater confidence in view of the fact that none of the postulated

additions to the present list of vitamins represents any strictly new concept such as might overturn our present views—they all represent rather the refinement of present views through subdivisions of existing concepts.

Thus a few years ago the refinement of knowledge of vitamin B led to its subdivision into two parts: a more heat-labile, now called vitamin B or B₁; and a more heat-stable, now called vitamin G or B₂. Each of these two parts is now apparently in process of being again subdivided, the first into B₁ and Reader's B₄¹; the second by the setting off of what Chick and Copping call the Y factor from the rest of vitamin G or B₂²—in each case a differentiation rather than the introduction of any radically new concept.

Secondly, two independent digests of the knowledge available up to about 1932, each representing a consensus of expert opinion, one British³ and the other American⁴, comprehending the clinical as well as the laboratory point of view, have recently made available a sufficiently well-balanced, well-matured body of subject-matter and interpretation, so that in many respects the physician can now feel that he has as well authenticated a basis for his practical judgments in matters respecting the vitamins as in many older fields.

In the British report, which explicitly states that every part of its text represents the study and judgment of all of its authors, it is stated that: "So far as Western civilization is concerned, it is no doubt true that the rareness of the occurrence of frank deficiency diseases, such as scurvy, xerophthalmia and beri-beri, indicates that an absolute deficiency of vitamins scarcely ever exists in the individual diet. On the other hand, it is now becoming generally recognized that much subnormal health and development, and even incidence of disease, are associated with a partial deficiency of one or more of these necessary substances. The influence of such partial deficiencies, even when relatively slight, may be extremely serious when they occur in early life . . . There is also danger that the effects of such

partial or latent deficiency may persist as a chronic condition throughout adult life." . . . And they emphasize the statement that, "*latent deficiency disease* is a real thing and not an imaginary concept."

In the volume issued by the American Medical Association, Mendel writes: "Existing knowledge permits little more than vague speculation respecting the mode of action of vitamin A . . . For the present it may be wiser to stress the indefinite function of the vitamin in preserving 'health and vigor' rather than to herald any specific action against definite microbiotic enemies. Deficiencies of any sort tend to decrease the ability of the body to resist disease." And in another article of the series, Eusterman and Wilbur, writing explicitly from the clinical standpoint say: "Until recently the versatility of vitamin A has apparently not been appreciated." Thus the fact that vitamin A is entirely specific among the vitamins in the sense that no other can take its place, is consistent with the fact that its function in serving the well-being of the body and as an *aid* to the ability to resist infection may be a more "versatile" or more generalized function than that of aiding against a single species of pathogen.

Hess, writing on vitamin C in the same series of articles says: "Another point that has been brought into prominence in connection with adult as well as infantile scurvy is its intimate association with the infectious process . . . one of the most striking and important symptoms of scurvy is a susceptibility to infection (furunculosis, nasal diphtheria, grippe, etc.)."

Thus while each vitamin is a specifically essential substance for which no other known substance can be substituted, yet shortages of certain vitamins may increase the body's susceptibility to more than one species of infection—yet, again, this does not mean to *all* infections equally.

A third general principle to be borne in mind is that, whatever therapeutic properties individual vitamins may possess, *a vitamin is primarily a nutritional factor.*

Thus in the introduction to a recent concise review contributed by the Department of Physiological Chemistry at Yale⁶ we read:

"The mass of pertinent experimental evidence at present available forces the conclusion that the conception of the vitamins is not a fad; indeed, it is rapidly ceasing to be looked upon even as a biochemical novelty but is rather accepted as one of the fundamental principles of nutrition."

Perhaps it should be emphasized, even at the risk of repetition—that the practitioner will often realize most satisfaction from thinking of the vitamins as nutrients rather than as drugs.

The British Committee's remark of some years ago upon the blurring of the nutritional significance by "pharmacological bias" still holds food for thought. Any practitioner may at any time be dealing with cases in which no vitamin can supply the specific pharmacodynamic action that is desired, yet in which whatever medication is employed will yield a more satisfactory result if attention is also given to the general nutritional well-being of the body by ensuring a liberal intake of any vitamin of which there may conceivably have been even a relative shortage. Thus, in the clinical article already referred to, Eusterman and Wilbur, after referring to the rarity of xerophthalmia in the United States, add: "It is likely, however, that certain individuals, the poor in particular, do not consume enough foods that contain vitamin A and vitamin G to insure a state of nutrition essential to the greatest physical stamina, efficiency, and ability to resist infectious diseases." And Wilder, in his address as Chairman of the Section on Pharmacology and Therapeutics at the Eighty-second Annual Session of the American Medical Association, referred to "the increasingly probable condition of mild or incipient avitaminosis" and further said: "I am convinced that many cases of dissatisfaction with treatment are accounted for by the partial starvation which results from incompletely balanced diets . . . In many

diseases the possibilities of therapeutic benefit from supplying nutritional elements in amounts greater than those required for maintenance in health is today receiving augmented attention."

Then too, the physician, in addition to employing the newer knowledge of nutrition not to supplant but rather to supplement his accustomed therapeutic methods, has also the opportunity to teach the patient (while *as patient* he or she is in a teachable frame of mind) how to acquire and maintain throughout the rest of life a nutritional condition superior to that which he would otherwise enjoy—or endure. The degree of well-being which is prevalent in the community need by no means be accepted as representing the physician's objective for his patient. No less high and conservative an authority than F. Gowland Hopkins has stated⁵ that, "a race or community is found in equilibrium with an environment which includes its food supply. It is often forgotten that such environment is fortuitous and that the equilibrium reached is one in which the community, while managing to survive, may yet be functioning at levels far below those possible to its innate capacities. It is truths of this sort that the science of nutrition, having reached the stage of controlled experiment, is now demonstrating." He also says:

"It is often felt that concerning matters so urgent as our own nutrition, humanity, with all the experience of the ages behind it, can have little to learn from modern science, yet, as in the case of so many other established traditions, an assumption of this kind is wholly unjustified. Tradition accumulates prejudices quite as often as truths, and the former are apt to be more potent in their influence." . . . And:

"That scientific research during recent years has greatly emphasized the importance of right nutrition as a factor in human welfare is very sure . . . We now know that conditions recognized as actual diseases develop because the supply of some minute nutritional necessity has failed, while, short of obvious disease, ill-health may depend upon

a lesser degree of such deficiency . . . In all individuals such a lack may greatly increase the liability to infection by bacteria and other parasites."

So much for the general consideration of the topic assigned me. The following brief statements regarding individual vitamins are all intended to be construed in the light of these general principles: (1) the highly specific nature of each vitamin in the sense that nothing else can take its place; (2) the possibility that a vitamin may nevertheless have a bearing upon the ability of the body to resist more than one species of infection; and (3) the general principle that a vitamin is primarily a nutritional rather than a pharmacological factor—and may, on that account, be all the more important to the physician who takes the long view of the well-being of the patient.

II.

SOME OBSERVATIONS WITH REFERENCE TO INDIVIDUAL VITAMINS

Vitamin A is a fat-soluble substance conspicuously essential to growth, and also very important to the maintenance of vigorous health at all ages.

In addition to the effect of vitamin A in maintaining, as the Journal of the American Medical Association puts it, the integrity of the body's first line of defence against infection, it also has a further influence. For in the carefully controlled experiments both of Lassen in Copenhagen and of Boynton and Bradford in Rochester, it was found that when infective organisms were introduced by injection so that the battle was staged entirely beyond the 'first line of defence', the ability of the body to resist the infection was again found much higher in the animals which had received the more liberal intakes of vitamin A. This is not necessarily a matter of the immunological mechanism as now understood; but it is a fact which we are probably not justified in ignoring, even if we cannot yet fully understand it.

Time does not permit more than the mention here of the very large amount of laboratory evidence that vitamin A taken in amounts above those which actual necessity requires, yields increasingly beneficial results in higher levels of vitality or standards of positive health.

Hess, Lewis, and Barenberg, in the *Journal of the American Medical Association* for August 26, 1933 discuss the question, "Does Our Dietary Require Vitamin A Supplement?" I think the answer should depend upon the dietary. Their controlled observations in a model child-caring home have not indicated decrease of respiratory infections as a result of increasing the intake of vitamin A above that which the dietary of the institution regularly afforded.

The 24 ounces of milk mentioned as regularly contained in their daily dietary probably by itself furnished each of these children well over 1500 International units of vitamin A per day; other articles of their liberal dietary enrich it still further in this respect; and these children probably entered the periods of controlled observation with fairly good stores of vitamin A already laid up in their bodies. A large proportion of the children of the United States and of New York City are less fortunate in these respects. May we therefore hope that the careful observations of Hess, Lewis and Barenberg will be interpreted to the credit of the nutritional condition of the children under their care, and not to the discredit of vitamin A?

Their findings constitute strong evidence against the exaggerated impressions which they and some others in this country and Harris and some others in England believe to be more or less prevalent; but perhaps it should be pointed out that where in such researches the evidence is conflicting, that which represents positive findings is usually fully as significant as that which is negative.

There is positive ("field") evidence of wide differences of vitamin A intake even among people of like economic status, depending upon their food habits, and there is also positive (laboratory) evidence that the dietaries richer in vitamin A tend to yield better results in the long run; but to avoid any possible misconception may I emphasize in the same sentence that I am speaking of such enrichment of vitamin A intake as may be had by the wise use of everyday articles of food?

Vitamin B (B₁). This is the substance the study of which as a preventive of beri-beri called general attention to the vitamin concept about 20 to 25 years ago. It was found that the neuritis of beri-beri could be prevented (and if not too far advanced could be cured) by many natural foods, and that from these foods a specific antineuritic substance could be extracted. The existence of this substance was established and the investigation of it was well advanced, before the coining of any such word as vitamin.

The outstanding characteristics of vitamin B are its antineuritic value and its value for the maintenance and promotion of appetite.

Its properties as a growth-essential and as in some way helping to keep the body in good tone and resistant to some types of infection, may be equally important but are less distinctive since some of the other vitamins also serve in such ways as these.

Speculations as to just "how it acts in the body" have perhaps been even more rife around vitamin B than about the other vitamins. Few if any of the other theories rest upon such substantial experimental evidence as does Cowgill's view^{4,6}, that while "the question of the exact function of this vitamin remains unsolved" there is a quantitative relation between the vitamin B requirement and the total energy metabolism or requirement. This point of view, with a full realization of the important influence

of vitamin B upon the appetite, may often be of therapeutic value. Varying circumstances may well lead to different answers in different cases as to when one should employ a vitamin B concentrate and when enrich the intake of vitamin B by increasing the proportion of the natural or less highly refined articles of food in the diet. The former will, of course, suggest itself in those cases in which a very large or very sudden increase is desired, while the latter has the advantage that it contributes to the enrichment of the intake of other important nutritional factors at the same time.

In the presence of Dr. Hess who has investigated so extensively both vitamins C and D and of Dr. Mendel whom we always wish to hear as often and as fully as opportunity permits, I shall but mention these two vitamins and then close with a few observations regarding vitamin G or B₂.

Vitamin C prevents and cures scurvy; but if we were sure that we should never see a case of scurvy we would still have ample reason to be interested in vitamin C. Hess has described how often children without distinctive scurvy symptoms are yet in need of more vitamin C in order to do their best. Wolbach, Howe and Church have shown the importance of vitamin C to the nutrition of the bones as well as of the soft tissues; and discussion in a recent issue of the Journal of the American Medical Association suggests that more liberal intake of vitamin C may perhaps be helpful in combating arthritis. Dolldorf relates it to capillary condition. Very likely our knowledge of the ways in which vitamin C serves the nutritional welfare of the body is still far from complete; yet already enough is known to suggest strongly that diets rich in vitamin C may be helpful in a wide variety of cases even if not specifically indicated by the symptoms observed.

Vitamin D is perhaps as dramatically effective against rickets as is vitamin C against scurvy. Is it, then, also a nutritional asset in which it is desirable to enrich the diet liberally at all ages? There are others present who can discuss this question better, so I leave it to them.

Vitamin G has so recently been differentiated from vitamin B that on many points much yet remains to be done to assess the relative responsibilities and merits of these two essential substances. It might be premature to assign to vitamin G any such clear-cut pharmacological function as that of vitamin B in the prevention and cure of beri-beri; but the suggested relationships of vitamin G both to pellagra and to pernicious anemia, and its recently demonstrated relation to the development of cataract all seem to call for careful consideration of the possibility that diets rich in vitamins A, C, and G may be helpful in a number of connections. We know that vitamin G has far-reaching effects on the well-being of our experimental animals.

Supplementing the summaries already mentioned (^{3,4,6}) reference may also be made to the still more recent summary paper of Day⁷.

As Day points out, Goldberger and Lillie⁸ were the first to describe the pathological condition in the rat due to a deficiency of what is now termed vitamin B₂ or G. Other laboratories soon confirmed and extended their general findings^{9,10,11,12,13}.

Goldberger and associates produced also an experimental condition known as black-tongue in dogs, and from similarities of symptoms (and their observations to the effect that all could be prevented or cured by the feeding of the same materials) they were led to suggest¹⁴ that pellagra in man, black-tongue in dogs, and the condition chiefly characterized by dermatitis in rats are all due to the same nutritional deficiency. In commenting upon this theory Underhill wrote⁴: "The discovery of the potency of the unknown factor termed vitamin G is an undoubted advance in the knowledge of pellagra, but it is clearly unwise to assume that vitamin G deficiency and pellagra are necessarily synonymous terms."

The caution thus suggested by Underhill would seem to be doubly justified, on the one hand by the developments in

the study of pellagra, and on the other by the fact that vitamin G deficiency is now known to give rise to other important effects in addition to the pellagra-like dermatitis.

Particularly important are the eye conditions described by Day and his coworkers^{7,15} and independently confirmed by O'Brien¹⁶ and by Yudkin¹⁷.

Thus vitamin G deficiency may be both less and more than clinical pellagra. Here as elsewhere, the attempt to assign the vitamin a physiologically or pharmacologically descriptive name is apt to throw undue emphasis upon what (however important in itself) is only one feature of its nutritional significance.

The work of Ellis in the writer's laboratory¹⁸ is affording strong evidence that a higher level of intake of vitamin G may distinctly influence the degree of nutritional well-being and resulting health and vitality, even though the lower intake is already above that at which any characteristic sign of nutritional deficiency appears.

We therefore believe that vitamin G not only prevents deficiency disease but has positive functions in normal nutrition as well, and that optimal nutrition requires a much more liberal intake of vitamin G than simply that which is demonstrably necessary for the prevention of any characteristic sign of deficiency.

In the foregoing discussion the term vitamin B or B₁ is allowed to stand for the whole of the more heat-labile, and the term vitamin B₂ or G for the whole of the more heat-stable, part of the vitamin B complex. The writer has no doubt that each of these two primary divisions of the vitamin-B complex is a multiple rather than a simple nutritional factor; but the necessity for brevity forbids the attempt to analyze the evidence in this paper. The nutritional considerations here briefly summarized will lose nothing of their significance when it becomes possible to assign them, or if necessary to reassign them, as properties of more precisely defined chemical substances.

As I began by saying that we have no definition of the vitamins, I may end by saying that we do not know how many vitamins there are. We have, however, good ground for believing that our present concepts cover the essentials and that further discoveries will be differentiations within the lines already well conceived; and will therefore not upset or supplant our present knowledge of the vitamins but rather supplement and refine it.

There is much knowledge now at hand which seems certainly sound so far as it goes; and I believe that it goes far enough to be capable of rendering good service to medicine, not only in remote contingencies but also in everyday practice.

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